ORIGINAL ARTICLE

Importance of Early COPD In Young Adults for Development of Clinical COPD

Findings from the Copenhagen General Population Study

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Abstract

Rationale: Individuals who will develop chronic obstructive pulmonary disease (COPD) could be identified at an early age before clinical manifestations appear.

Objectives: We investigated risk of clinical COPD 10 years later in young adults from the general population with and without early COPD with a focus on smoking exposure.

Methods: We included 14,870 individuals aged 20–100 years from the Copenhagen General Population Study with spirometry 10 years apart. Early COPD was defined as baseline FEV_1/FVC less than the lower limit of normal in individuals aged <50 years. Outcomes included clinical COPD at final examination 10 years later (chronic respiratory symptoms with FEV_1/FVC <0.70 and FEV_1 <80% predicted) and acute exacerbation hospitalizations during follow-up.

Measurements and Main Results: Among 5,497 individuals aged <50 years at baseline with FEV_1/FVC ⩾0.70, 104 (3%) developed clinical COPD 10 years later; 4% of smokers with ⩾10 pack-years had early COPD; 3% of smokers with <10 pack-years had early COPD; and 2% of never-smokers had early COPD. Among smokers with ⩾10 pack-years, 24% developed clinical COPD in those with early COPD versus 4% in those without early COPD. Corresponding numbers were 10% and 1% in smokers with <10 pack-years and 3% and <1% in never-smokers, respectively. Among individuals with early COPD, odds ratios for clinical COPD 10 years later were 7.77 (95% confidence interval [CI], 4.10–14.7) in smokers with ⩾10 pack-years and 8.56 (95% CI, 4.92–14.9) in all smokers, whereas hazard ratios for acute exacerbation hospitalizations were 4.16 (95% CI, 1.66–10.5) and 4.33 (95% CI, 1.89–9.93), respectively. Results were validated in the Copenhagen City Heart Study.

Conclusions: Depending on amount of smoking exposure, <24% of young adults in the general population with early COPD develop clinical COPD 10 years later. A smoking exposure threshold for early COPD should be reconsidered, as younger individuals are less represented in those with high smoking exposure.

Keywords: early diagnosis; airway obstruction; forced expiratory volume; spirometry; early disease

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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At a Glance Commentary

Scientific Knowledge on the Subject: Individuals who will develop chronic obstructive pulmonary disease (COPD) could be identified at an early age before disease onset, allowing for the implementation of preventive measures and thereby halting progression. Recently, an international group of experts proposed an operational definition for early COPD in individuals aged <50 years.

What This Study Adds to the Field: We investigated risk of clinical COPD 10 years later in young adults from the general population with and without early COPD, with a focus on smoking exposure. Early COPD, defined as FEV_1/FVC less than the lower limit of normal in individuals aged <50 years at baseline examination, was present in 4% of smokers with ⩾10 pack-years, 3% of smokers with <10 pack-years, and 2% of never-smokers. Among smokers with ⩾10 pack-years, 24% developed clinical COPD at final examination 10 years later in those with early COPD versus 4% in those without early COPD. Corresponding numbers were 10% and 1% in smokers with <10 pack-years and 3% and <1% in never-smokers, respectively. Ignoring smoking quantity in those with early COPD dropped sensitivity slightly without affecting specificity or positive or negative predictive values and did not change risk of clinical COPD 10 years later or acute exacerbation hospitalizations during follow-up.

Chronic obstructive pulmonary disease (COPD) is prevalent in middle-aged and older adults associated with significant morbidity and mortality (1). Nonetheless, it is increasingly evident that COPD has its origins in early life and develops over the course of many years (2–6). Individuals who will develop COPD could be identified at an early age before disease onset, allowing for the implementation of preventive measures and thereby halting progression (7). However, over the last decades, research on COPD has mainly focused on older patients with established severe disease, as these comprise a significant proportion of the clinical consultations.

To facilitate more research on the early origins of COPD, an international group of experts proposed an operational definition of early COPD by distinguishing "early" from "mild" disease (8). Accordingly, early COPD should be defined in individuals aged <50 years with a smoking exposure ⩾10 pack-years with one or more of the following: *1*) FEV_1/FVC less than the lower limit of normal (LLN), *2*) compatible computed tomographic (CT) abnormalities (i.e., visual emphysema, air trapping, or bronchial thickening graded mild or worse), and/or *3*) evidence of accelerated FEV_1 decline of ⩾60 ml/yr. Recently, we found that 15% of the general population (defined as FEV_1/FVC less than the LLN in individuals aged <50 yr with smoking exposure ⩾10 pack-years) fulfill criteria of early COPD (9). Furthermore, individuals with early COPD had an increased risk of acute respiratory hospitalizations and early death. Nonetheless, it is still uncertain whether young adults identified with early COPD will subsequently develop clinical COPD during follow-up. In addition, because never-smokers and smokers with low smoking exposure may also develop COPD (10–13), it would also be relevant to investigate the presence of early COPD and subsequent clinical COPD development in these individuals.

We investigated the risk of clinical COPD 10 years later in young adults from the general population with and without early COPD, with a focus on smoking exposure. For this purpose, we used the Copenhagen General Population Study, a Danish contemporary population-based cohort study. For independent validation, we used the Copenhagen City Heart Study, another Danish population-based cohort study.

Methods

Study Design and Population

We recruited individuals aged 20–100 years from the Copenhagen General Population Study, a Danish population-based cohort study with ongoing enrollment (9, 14–16). In Denmark, all individuals are assigned a unique identification number (Central Person Registration number) at birth or immigration and are recorded in the national Danish Civil Registration System. Individuals living in the capital region of Denmark were randomly invited from the national Danish Civil Registration System to reflect the adult Danish population (response rate, 43%). All participants completed a questionnaire, underwent a physical examination, and provided blood for biochemical analyses. Questionnaires were reviewed at the day of attendance by a healthcare professional together with the participant. The study was approved by Herlev and Gentofte Hospital and the regional ethics committee (approval number H-KF-01-144/01) and was conducted according to the Declaration of Helsinki. All participants provided written informed consent. In the present study, we included individuals with complete information on lung function and smoking exposure at baseline examination recruited from November 26, 2003, to April 28, 2015. An ongoing follow-up examination was initiated on March 31, 2014, in which individuals are invited systematically based on region and previous participation date, thereby allowing an approximate follow-up time of 10 years (17).

Definition of Early COPD and Smoking Exposure

Date of birth was obtained from the national Danish Civil Registration System. Prebronchodilator FEV_1 and FVC were measured at baseline and final examination. Spirometry use in the Copenhagen General Population Study has undergone a rigorous validation process (18). Predicted values were calculated according to national Danish lung function reference equations, which are based on 11,288 healthy asymptomatic never-smoking individuals, with age and height as covariates separately for men and women (18). The LLN, defined as the bottom fifth percentile of the predicted value, was calculated as the mean value minus 1.645 SDs. Detailed descriptions of lung function procedures, chronic respiratory symptoms, and other characteristics are provided in the online supplement. Early COPD was defined as a FEV_1/FVC less than the LLN in individuals aged <50 years at the baseline examination. Individuals with FEV_1/FVC of <0.70 at the baseline examination were excluded (Figure 1).

Information on smoking exposure was obtained from the questionnaire. Smoking status was defined as never, former, or current smoking. Tobacco consumption was

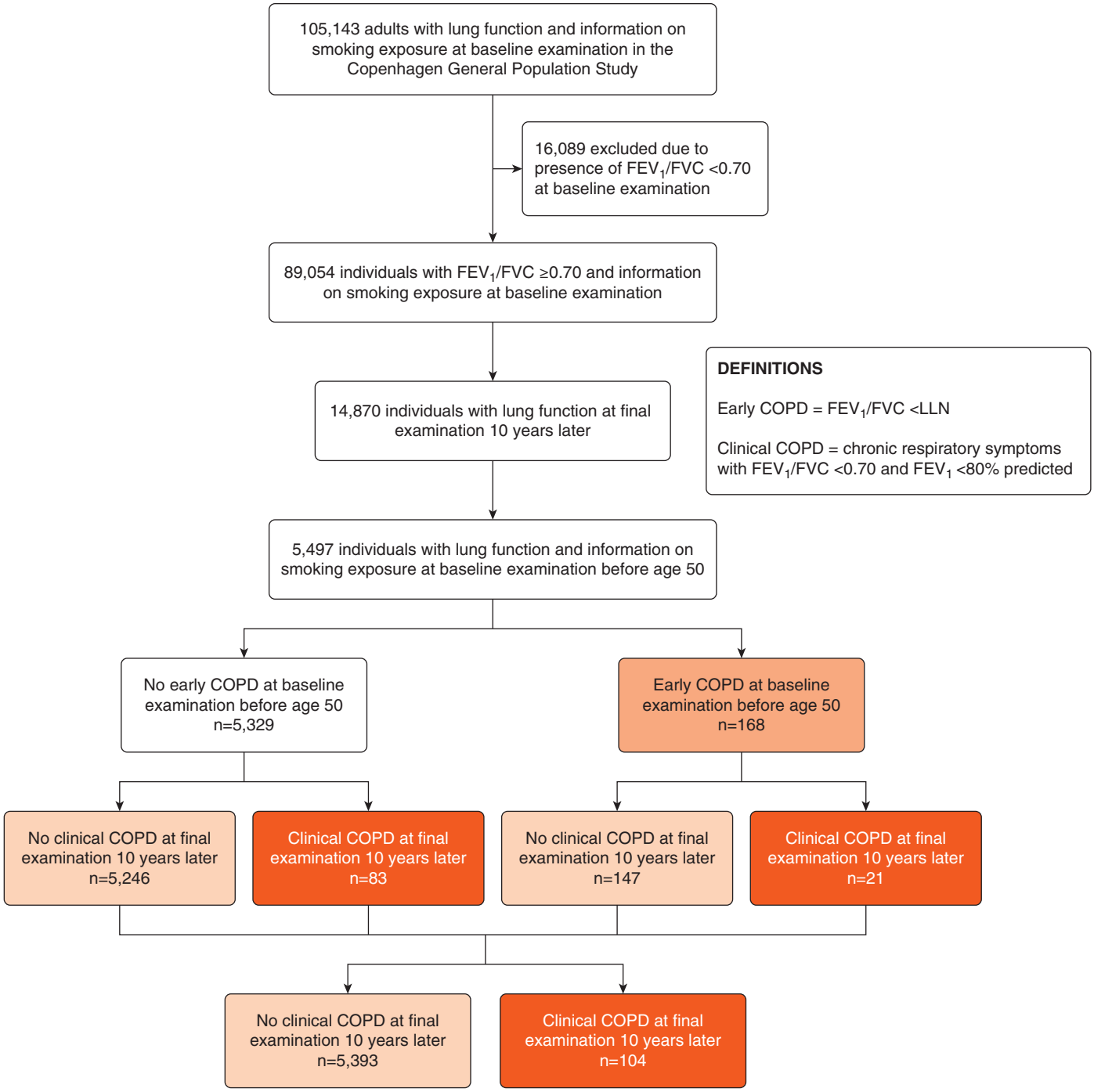

Figure 1. Study population. COPD = chronic obstructive pulmonary disease; LLN = lower limit of normal.

calculated in pack-years on the basis of information on age at smoking initiation and cessation (or for current smokers, until age at baseline examination), duration of tobacco consumption, and amount of consumed tobacco in the form of number of daily consumed cigarettes, cheroots, and cigars and grams of weekly consumed pipe tobacco (one cheroot = 3 g of tobacco, one cigar = 5 g of tobacco, and 1 g of tobacco = one cigarette); 1 pack-year was defined as 20 cigarettes or equivalent smoked daily for 1 year (9). Individuals with and without early COPD were subsequently stratified according to smoking exposure, as follows: smokers with ⩾10 pack-years, smokers with <10 pack-years, and never-smokers. Never-smokers included only individuals reporting not to have smoked throughout life.

Outcomes

Clinical COPD was defined as chronic respiratory symptoms with FEV_1/FVC of <0.70 and FEV_1 <80% predicted at the final

examination 10 years later. Chronic respiratory symptoms included chronic mucus hypersecretion, dyspnea, wheezing, and/or cough. Acute exacerbation hospitalizations during follow-up included all emergency department visits and hospital admissions with a primary discharge diagnosis of obstructive lung disease (International Classification of Diseases [ICD]-10 J41–J46) (9). Information was available from the national Danish Patient Registry, which covers all public and private hospital contacts in Denmark, recorded from baseline examination until April 10, 2018. Because follow-up was done by combining the national Danish Patient Registry with the national Danish Civil Registration System through the unique Central Person Registration number provided to everyone at birth or immigration, no person was lost to follow-up, and individuals who emigrated were censored at the date of emigration ($n = 442$). All diagnoses recorded in the national Danish Patient Registry are made by a medical doctor according to national Danish laws using the World Health Organization ICD codes.

Independent Validation

For independent external validation, we used the Copenhagen City Heart Study, another Danish population-based cohort study that was initiated in 1976–1978 with follow-up examinations in 1981–1983, 1991–1994, and 2001–2003; it was recruited and examined as in the Copenhagen General Population Study but from different parts of Copenhagen (19). Because we needed a comparable time of follow-up with that of the Copenhagen General Population Study, we used information on lung function and smoking exposure from the 1981–1983, 1991–1994, and 2001–2003 examinations (i.e., we followed individuals from 1981–1983 through 1991–1994 and individuals from 1991–1994 through 2001–2003). Clinical COPD at final examination 10 years later and acute exacerbation hospitalizations during follow-up (also including ICD-8 491–493) were defined similarly as in the Copenhagen General Population Study. Denmark used the ICD-8 until January 1, 1994, and proceeded directly to ICD-10 thereafter. Again, individuals with FEV_1/FVC of <0.70 at baseline examination were excluded (805 of 8,324). No individual appeared in more than one study. Detailed descriptions of lung function procedures and chronic respiratory symptoms in the Copenhagen City Heart Study are provided in the online supplement.

Statistical Analyses

Wilcoxon's rank-sum or Pearson's χ^2 tests were used for group comparisons. Sensitivity, specificity, and positive and negative predictive values for clinical COPD at final examination 10 years later were estimated in individuals with early COPD with varying smoking exposure at the baseline examination. Kernel density estimation was used to illustrate the relative age distribution. Logistic regression was used to determine the risk of clinical COPD at the final examination. Cox regression was used to determine the risk of acute exacerbation hospitalizations during follow-up using multiple failure-time analyses according to a marginal means/rates model (i.e., individuals were at risk of recurrent events) (20). To avoid counting a single event multiple times, we decided that during follow up, hospitalized individuals had to be clinically stable for at least 4 weeks after discharge before they were at risk for a subsequent event, in accordance with previous recommendations (21–24). Although the predictive capability for clinical COPD at final examination was investigated by determining area under the curve for the receiver operating characteristics, the predictive capability for acute exacerbation hospitalizations during follow-up was investigated by determining Harrell's C statistic. Analyses were performed using STATA/SE 13.1 for Windows (StataCorp), and a two-sided P value <0.05 was considered significant.

Results

Among 89,054 adults with FEV_1/FVC ≥ 0.70 and information on smoking exposure at baseline examination from the Copenhagen General Population Study, 14,870 had lung function measurement at the final examination 10 years later (Figure 1). Among these 14,870 individuals, 5,497 were aged <50 years at the baseline examination, of whom, 168 (3%) had early COPD, which was defined as FEV_1/FVC less than the LLN. At the final examination 10 years later, of 5,497 individuals, 104 (2%) had developed clinical COPD, which defined as chronic respiratory symptoms with FEV_1/FVC of <0.70 and FEV_1 $<80\%$ predicted. Among all individuals, those without lung function information versus those with lung function information at final examination had a higher baseline age, which may explain the higher death rate during follow-up, as the two groups only differed slightly when comparing baseline lung function, smoking exposure, and chronic respiratory symptoms (*see* Table E1 in the online supplement). In contrast, all these differences were minute when comparing among individuals aged <50 years at baseline examination (Table E2).

Characteristics of Early COPD

At baseline examination, individuals with early COPD had lower lung function (FEV_1 2.91 L vs. 3.40 L) and reported more frequent symptoms (50% versus 36%) and slightly higher smoking exposure (13.7 pack-years vs. 10.5 pack-years) compared with individuals without early COPD (Table 1). During follow-up, individuals with early COPD did not differ from those without early COPD in regard to FEV_1 decline (23 ml/yr vs. 22 ml/yr). FEV_1 decline ≥ 60 ml/yr was 8% in those with early COPD compared with 6% in those without early COPD. Among individuals with and without early COPD, the number of active smokers decreased, whereas the number of former smokers increased during 10 years of follow-up.

Exploring Age Distribution

When age distribution was investigated in individuals aged <50 years at baseline examination, we found that younger individuals were less represented in those with smoking exposure ≥ 10 pack-years (Figure 2). Among 5,497 individuals, 20% were aged 20–39 years, and 80% were aged 40–49 years. Corresponding numbers were 25% and 75% in those with FEV_1/FVC less than the LLN, 14% and 86% in those with smoking exposure ≥ 10 pack-years, and 16% and 84% in those with both FEV_1/FVC less than the LLN and smoking exposure ≥ 10 pack-years, respectively.

Characteristics of Clinical COPD

At baseline examination before age 50, individuals with subsequent clinical COPD were slightly older (46.2 yr vs. 44.1 yr), had lower lung function (FEV_1 2.60 L vs. 3.40 L), and more often reported asthma (16% vs. 6%) and symptoms (76% vs. 36%) compared with individuals without clinical COPD (Table 2). In addition, more than half of them were active smokers, and already at baseline examination, 53% had an FEV_1

Table 1. Characteristics of Individuals with and without Early COPD at Baseline Examination in the Copenhagen General Population Study

	No Early COPD at Baseline Examination (*n* = *5,329*)	Early COPD at Baseline Examination (*n* = *168*)
At baseline examination before age 50		
Age, yr	44.1 (40.9–47.0)	43.1 (40.0–46.4)*
Sex, M, *n* (%)	2,151 (40)	58 (35)
Lung function		
FEV_1, L	3.40 (2.94–4.01)	2.91 (2.65–3.43)*
FEV_1% predicted, %	98 (90–106)	89 (81–96)*
$FEV_1 < 80$% predicted, *n* (%)	319 (6)	37 (22)*
FVC, L	4.20 (3.62–4.96)	4.10 (3.73–4.89)
FVC% predicted, %	98 (90–106)	103 (93–110)*
FEV_1/FVC	0.81 (0.78–0.84)	0.71 (0.70–0.72)*
$FEV_1/FVC < 0.70$, *n* (%)	0 (0)	0 (0)
Smoking information		
Never-smokers, *n* (%)	2,719 (51)	65 (39)*
Former smokers, *n* (%)	1636 (31)	56 (33)
Current smokers, *n* (%)	961 (18)	47 (28)*
Unknown smokers, *n* (%)	13 (<1)	0 (0)
Smoking exposure, pack-years†	10.5 (4.5–20.0)	13.7 (5.0–27.0)*
Asthma, *n* (%)	311 (6)	24 (14)*
Treatment with airway medication, *n* (%)	210 (4)	19 (11)*
Symptoms, *n* (%)		
Chronic mucus hypersecretion	278 (5)	19 (11)*
Dyspnea	1,252 (23)	51 (30)*
mMRC ⩾ 2	170 (3)	6 (4)
Nighttime dyspnea	172 (3)	8 (5)
Wheezing	872 (16)	51 (30)*
Cough	657 (12)	31 (18)*
Any symptom	1,938 (36)	84 (50)*
At final examination 10 yr later		
Age, yr	54.3 (50.9–57.2)	52.9 (49.9–56.6)*
Lung function		
FEV_1, L	3.16 (2.71–3.82)	2.73 (2.40–3.20)*
FEV_1% predicted, %	100 (91–108)	89 (81–97)*
Annual decline in FEV_1, ml/yr	22 (6–37)	23 (6–40)
Annual decline in $FEV_1 \geqslant 60$ ml/yr, *n* (%)	333 (6)	14 (8)
Total decline in FEV_1, ml	219 (63–372)	230 (55–400)
FVC, L	4.11 (3.56–4.97)	4.05 (3.52–4.74)
FVC% predicted, %	104 (96–112)	104 (96–113)
FEV_1/FVC	0.77 (0.73–0.80)	0.68 (0.65–0.72)*
Smoking information		
Never-smokers, *n* (%)	2,671 (50)	64 (38)*
Former smokers, *n* (%)	2,044 (38)	73 (43)
Current smokers, *n* (%)	568 (11)	30 (18)*
Unknown smokers, *n* (%)	46 (<1)	1 (<1)
Smoking exposure, pack-years†	11.3 (5.0–22.5)	16.5 (5.6–30.0)*
Asthma, *n* (%)	416 (8)	30 (18)*
Treatment with airway medication, *n* (%)	182 (3)	18 (11)*
Symptoms, *n* (%)		
Chronic mucus hypersecretion	340 (6)	10 (6)
Dyspnea	1,371 (26)	60 (36)*
mMRC ⩾ 2	202 (4)	4 (2)
Nighttime dyspnea	130 (2)	6 (4)
Wheezing	662 (12)	32 (19)*
Cough	304 (6)	9 (5)
Any symptom	1,864 (35)	74 (44)*

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; mMRC = modified Medical Research Council dyspnea scale. Data are presented as median (25th–75th percentile) or *n* (%). Early COPD was defined as FEV_1/FVC less than the lower limit of normal in individuals aged <50 years at baseline examination.

*$P < 0.05$ for comparison with individuals without early COPD using Wilcoxon's rank-sum or Pearson's χ^2 test.

†Includes only smokers.

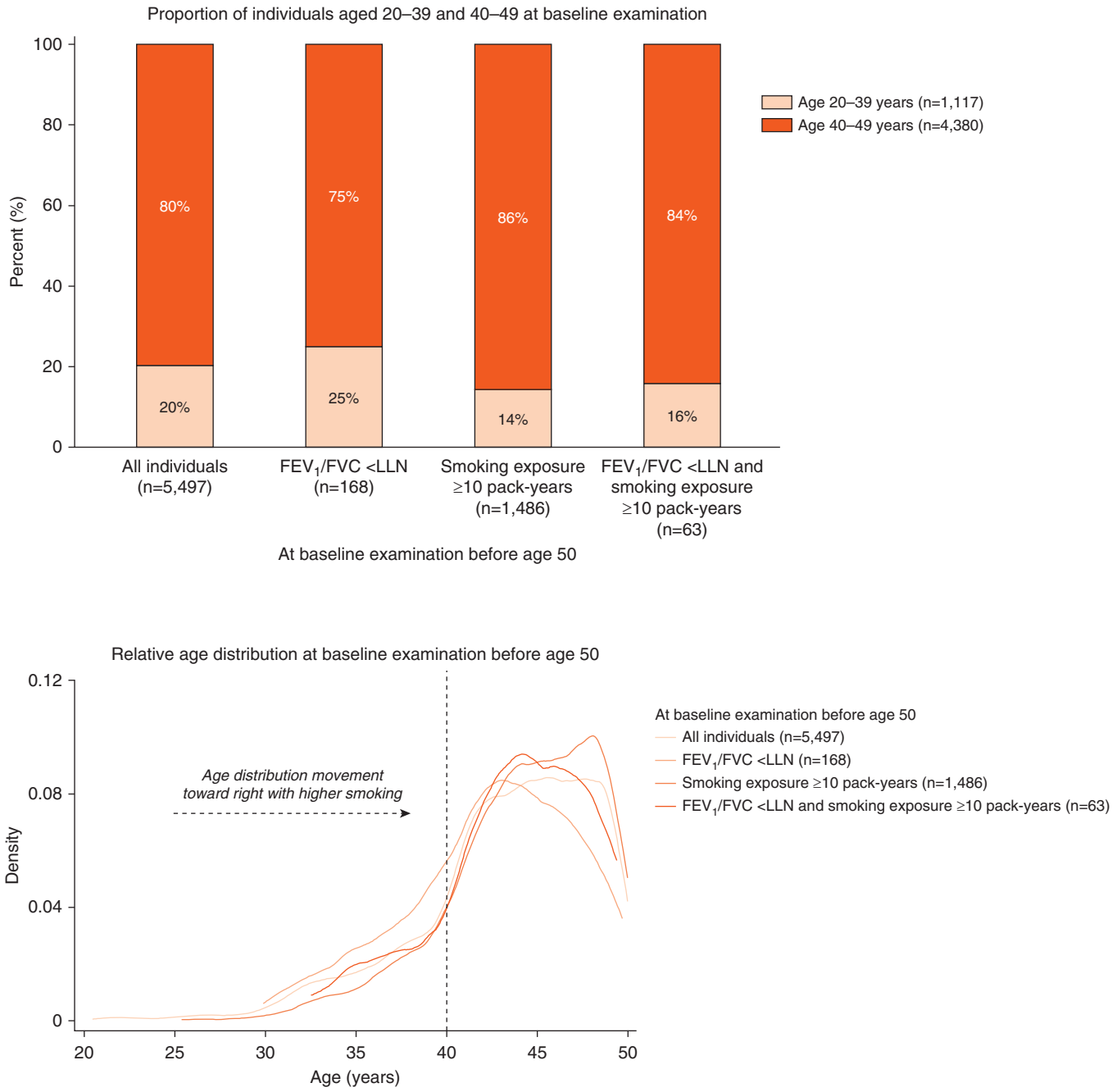

Figure 2. Age composition at baseline examination before age 50. Data are based on the Copenhagen General Population Study. LLN = lower limit of normal.

<80% predicted despite an FEV_1/FVC ⩾0.70. During follow-up, individuals with subsequent clinical COPD had an FEV_1 decline of 45 ml/yr (31% with FEV_1 decline ⩾60 ml/yr), whereas individuals without clinical COPD had an FEV_1 decline of 21 ml/yr (6% with FEV_1 decline ⩾60 ml/yr). Among both individuals with clinical COPD and individuals without clinical COPD, the number of active smokers decreased during 10 years of follow-up.

Impact of Smoking Exposure in Individuals with Early COPD

At baseline examination, prevalence of early COPD before age 50 was 4% in smokers with ⩾10 pack-years, 3% in smokers with <10 pack-years, and 2% in never-smokers (Figure 3, left). At final examination 10 years later in smokers with ⩾10 pack-years, 24% developed clinical COPD in those with early COPD versus 4% in those without early COPD (Figure 3, right). Corresponding numbers were 10% and 1% in smokers with <10 pack-years and 3% and <1% in never-smokers, respectively.

Table 2. Characteristics of Individuals with and without Clinical COPD at Final Examination in the Copenhagen General Population Study

	No Clinical COPD at Final Examination (*n* = *5,393*)	Clinical COPD at Final Examination (*n* = *104*)
At baseline examination before age 50		
Age, yr	44.1 (40.8–47.0)	46.2 (44.0–47.7)*
Sex, M, *n* (%)	2,169 (40)	40 (38)
Lung function		
FEV_1, L	3.40 (2.94–4.01)	2.60 (2.32–3.09)*
FEV_1% predicted, %	98 (90–106)	79 (72–85)*
$FEV_1 < 80$% predicted, *n* (%)	301 (6)	55 (53)*
FVC, L	4.20 (3.64–4.97)	3.48 (3.07–4.25)*
FVC% predicted, %	99 (91–107)	86 (78–93)*
FEV_1/FVC	0.81 (0.77–0.84)	0.74 (0.72–0.77)*
$FEV_1/FVC < 0.70$, *n* (%)	0 (0)	0 (0)
Smoking information		
Never-smokers, *n* (%)	2,766 (51)	18 (17)*
Former smokers, *n* (%)	1,667 (31)	25 (24)
Current smokers, *n* (%)	947 (18)	61 (59)*
Unknown smokers, *n* (%)	13 (<1)	0 (0)
Smoking exposure, pack-years†	10.0 (4.4–20.0)	25.0 (16.3–33.0)*
Asthma, *n* (%)	319 (6)	16 (15)*
Treatment with airway medication, *n* (%)	212 (4)	17 (16)*
Symptoms, *n* (%)		
Chronic mucus hypersecretion	270 (5)	27 (26)*
Dyspnea	1,247 (23)	56 (54)*
mMRC ⩾ 2	160 (3)	16 (15)*
Nighttime dyspnea	172 (3)	8 (8)*
Wheezing)	872 (16)	51 (49)*
Cough	651 (12)	37 (36)*
Any symptom	1,943 (36)	79 (76)*
At final examination 10 yr later		
Age, yr	54.2 (50.8–57.2)	56.5 (54.3–58.1)*
Lung function		
FEV_1, L	3.16 (2.72–3.82)	2.13 (1.97–2.52)*
FEV_1% predicted, %	100 (92–108)	73 (67–77)*
Annual decline in FEV_1, ml/yr	21 (6–36)	45 (28–66)*
Annual decline in $FEV_1 \geqslant 60$ ml/yr, *n* (%)	315 (6)	32 (31)*
Total decline in FEV_1, ml	220 (60–370)	450 (310–685)*
FVC, L	4.12 (3.58–4.98)	3.29 (2.94–4.01)*
FVC % predicted, %	104 (96–113)	89 (82–94)*
FEV_1/FVC	0.77 (0.73–0.80)	0.66 (0.62–0.68)*
Smoking information		
Never-smokers, *n* (%)	2,719 (50)	16 (15)*
Former smokers, *n* (%)	2,076 (38)	41 (39)
Current smokers, *n* (%)	552 (10)	46 (44)*
Unknown smokers, *n* (%)	46 (<1)	1 (<1)
Smoking exposure, pack-years†	11.2 (4.9–22.5)	27.0 (20.0–40.0)*
Asthma, *n* (%)	425 (8)	21 (20)*
Treatment with airway medication, *n* (%)	181 (3)	19 (18)*
Symptoms, *n* (%)		
Chronic mucus hypersecretion	316 (6)	34 (33)*
Dyspnea	1,351 (25)	80 (77)*
mMRC ⩾ 2	185 (3)	21 (20)*
Nighttime dyspnea	133 (2)	3 (3)
Wheezing	637 (12)	57 (55)*
Cough	280 (5)	33 (32)*
Any symptom	1,834 (34)	104 (100)*

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; mMRC = modified Medical Research Council dyspnea scale.
Data are presented as median (25th–75th percentile), or *n* (%). Clinical COPD was defined as chronic respiratory symptoms with FEV_1/FVC of <0.70 and $FEV_1 < 80$% predicted at final examination 10 years later. Chronic respiratory symptoms included chronic mucus hypersecretion, dyspnea, wheezing, and/or cough.
*$P < 0.05$ for comparison with individuals without clinical COPD using Wilcoxon's rank-sum or Pearson's χ^2 test.
†Includes only smokers.

Presence of early COPD in smokers with ⩾10 pack-years at baseline examination before age 50 yielded a sensitivity of 24%, a specificity of 96%, a positive predictive value of 21%, and a negative predictive value of 97% for predicting clinical COPD at final examination 10 years later (Table 3). Interestingly, when the presence of early COPD was investigated in all smokers (thereby ignoring smoking quantity), sensitivity only dropped slightly from 24% to 18%, without any noteworthy change in specificity, or in positive or negative predictive values. Sensitivity dropped to 13% when never-smokers were also included, without any large change in the other values. Results were similar when clinical COPD was defined using LLN (compare Table 3 with Table E3). A combination of baseline lung function and smoking exposure yielded a higher predictive capability for subsequent clinical COPD development than lung function and smoking exposure separately (Figure E1).

Risk of Clinical COPD and Acute Exacerbation Hospitalizations

In individuals with early COPD at baseline examination, risk of clinical COPD at final examination 10 years later and risk of acute exacerbation hospitalizations during follow-up did not differ substantially between smokers with ⩾10 pack-years and all smokers (Figure 4, top). Among individuals with early COPD, odds ratios (ORs) for clinical COPD were 7.77 (95% confidence interval [CI], 4.10–14.7) in smokers with ⩾10 pack-years and 8.56 (95% CI, 4.92–14.9) in all smokers. Corresponding hazard ratios (HRs) for acute exacerbation hospitalization were 4.16 (95% CI, 1.66–10.5) and 4.33 (95% CI, 1.89–9.93), respectively. The predictive capability of early COPD for clinical COPD and for acute exacerbation hospitalizations was slightly higher in smokers with ⩾10 pack-years than in all smokers (Figure E2, top).

Independent Validation in the Copenhagen City Heart Study

Results were similar in the Copenhagen City Heart Study (Figures 4 and E2, bottom). ORs for clinical COPD at final examination were 11.4 (95% CI, 6.83–19.1) in smokers with ⩾10 pack-years and 11.1 (95% CI, 6.90–17.9) in all smokers. Corresponding HRs for acute exacerbation hospitalization were 3.90 (95% CI, 1.83–8.32) and 4.26 (95% CI, 2.06–8.80), respectively.

Discussion

Early COPD, defined as FEV_1/FVC less than the LLN in individuals aged <50 years at baseline examination, was present in 4% of smokers with ⩾10 pack-years, in 3% of smokers with <10 pack-years, and in 2% of never-smokers. Among smokers with ⩾10 pack-years, 24% of those with early COPD developed clinical COPD at final examination 10 years later versus 4% in those without early COPD. Corresponding numbers were 10% and 1% in smokers with <10 pack-years and 3% and <1% in never-smokers, respectively. Among individuals with early COPD, younger individuals were less represented in smokers with ⩾10 pack-years. Ignoring smoking quantity in those with early COPD dropped sensitivity slightly without affecting specificity or positive or negative predictive values and did not change the risk of clinical COPD 10 years later or acute exacerbation hospitalizations during follow-up.

Depending on the amount of smoking exposure, <24% of individuals defined with early COPD at baseline examination before age 50 developed clinical COPD at final examination 10 years later. This clearly demonstrates how difficult it is to define early COPD among younger individuals as well as the potential for overdiagnosis. Interestingly, we observed very high negative predictive value of 97% irrespective of smoking exposure, suggesting that the proposed operational definition for early COPD may be good at excluding individuals not likely to develop clinical COPD later in life. Indeed, <4% of individuals without early COPD at baseline developed clinical COPD subsequently. Nonetheless, we need to identify factors that can better determine why some individuals develop COPD and why some do not. A good starting point would be investigations in individuals with early COPD who develop clinical COPD later in life.

The recently proposed operational definition for early COPD includes ⩾10 pack-years of smoking exposure as a requirement in individuals aged <50 years. However, younger individuals were less represented in smokers with ⩾10 pack-years among those with early COPD. This should not be surprising, as it would take a longer time for an average smoker to obtain a higher cumulative tobacco consumption, thereby moving the age distribution toward a higher age. Consequently, the probability of capturing very early phases of disease development will be reduced. Furthermore, never-smokers and smokers with low tobacco consumption may also develop COPD (10–13), which we also found in the present study.

Acceleration of normal age-related decline of lung function is an important pathogenic mechanism for COPD development and progression (6, 25). Evidence of accelerated FEV_1 decline of ⩾60 ml/yr has also been proposed as a criterion in the operational definition of early COPD (8). During follow-up, 31% individuals with clinical COPD had experienced an FEV_1 decline of ⩾60 ml/yr versus 6% in those without clinical COPD. Although we could have used accelerated decline in the definition of early COPD, we believe that it is difficult to apply in a primary care setting, in which the quality of spirometry may vary. Multiple measurements over longer periods of time are required to accurately determine the decline, which again will delay diagnosis and potential intervention before disease onset.

In contrast, visual emphysema, air trapping, and/or bronchial thickening could potentially be identified using chest CT imaging, also proposed in the operational definition of early COPD (8). Unfortunately, we did not have such information and have therefore likely missed some individuals with CT abnormalities despite normal spirometry, suggesting the presence of early COPD (26, 27). Because <4% of individuals with normal spirometry developed subsequent clinical COPD, we believe that results would be largely similar if we had information on CT abnormalities. However, if CT findings became part of the diagnosis of COPD as suggested recently (28), this could probably improve diagnostic discrimination.

It is now increasingly evident that COPD development follows several lung function trajectories; some cases develop because of an accelerated lung function decline, whereas others do not achieve the expected maximally attained lung function in early adulthood and, either as a result of this or because of subsequent exposures, develop airflow limitation (6, 29). Interestingly, we observed that individuals with early COPD had a similar FEV_1 decline as those without early COPD, suggesting that the lung function trajectory characterized by interference with normal lung development and growth may be more predominant in

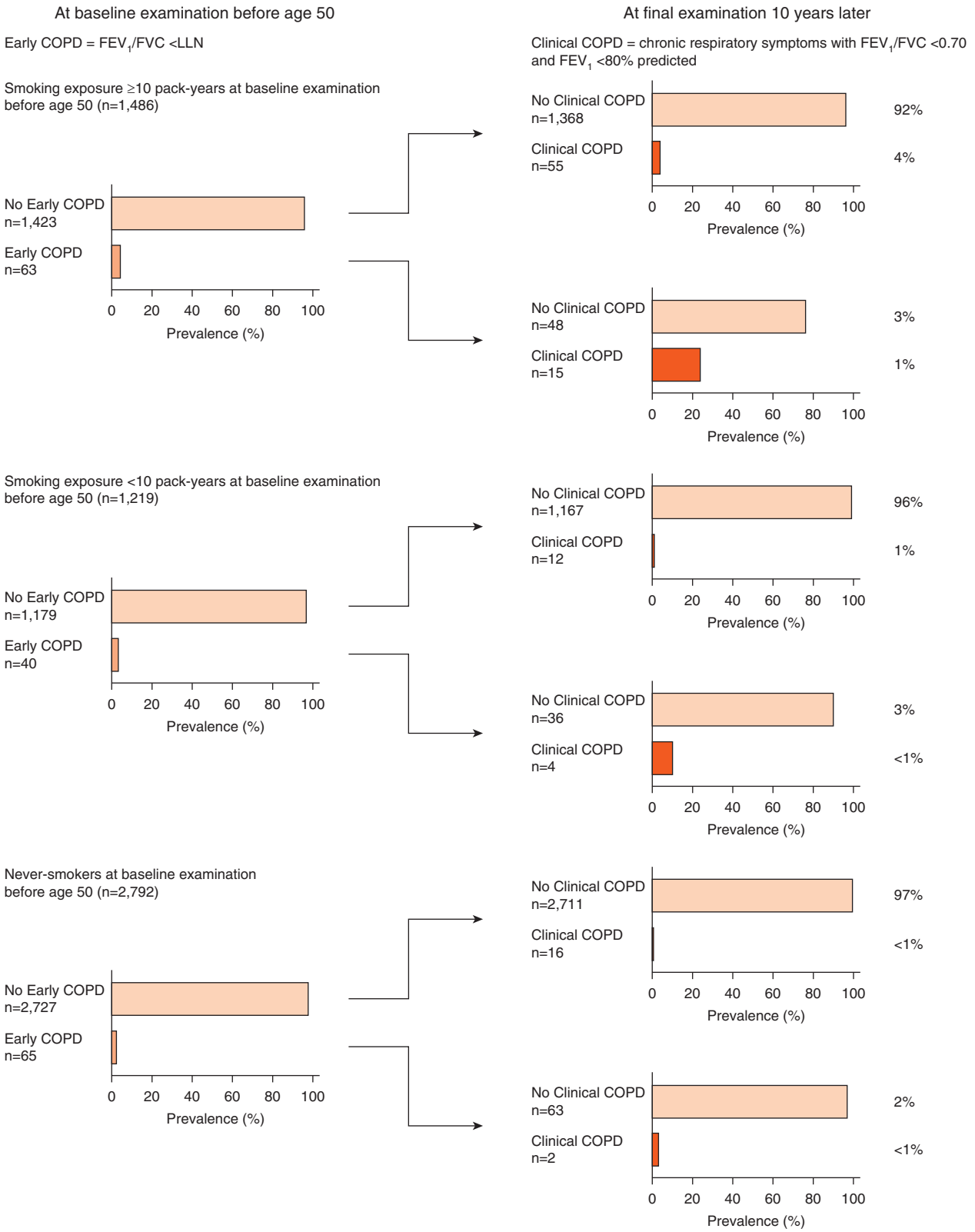

Figure 3. Early chronic obstructive pulmonary disease (COPD) at baseline examination before age 50 and development of clinical COPD at final examination 10 years later. Chronic respiratory symptoms included chronic mucus hypersecretion, dyspnea, wheezing, and/or cough. Absolute prevalence indicated at the far right. Data are based on the Copenhagen General Population Study. LLN = lower limit of normal.

Table 3. Predicting Clinical COPD at Final Examination 10 Years Later in Individuals with Early COPD at Baseline Examination before Age 50

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Smokers with ⩾10 pack-years ($n = 1,486$)	24	96	21	97
Smokers with ⩾7.5 pack-years ($n = 1,720$)	25	96	22	97
Smokers with ⩾5 pack-years ($n = 1,997$)	22	97	21	97
Smokers with ⩾2.5 pack-years ($n = 2,313$)	20	97	22	97
All smokers ignoring smoking quantity ($n = 2,705$)	18	97	22	97
All individuals including never-smokers ($n = 5,497$)	13	98	20	97

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.
Clinical COPD was defined as chronic respiratory symptoms with FEV_1/FVC of <0.70 and $FEV_1 < 80\%$ predicted at final examination 10 years later. Chronic respiratory symptoms included chronic mucus hypersecretion, dyspnea, wheezing, and/or cough. Early COPD was defined as FEV_1/FVC less than the lower limit of normal in individuals aged <50 years at baseline examination. Data are based on the Copenhagen General Population Study.

these individuals. For comparison, individuals with clinical COPD had higher FEV_1 decline. Early life factors predisposing to COPD may include low birth weight and/or prematurity, passive parental smoking exposure, and childhood respiratory tract infections and asthma (30). Asthma prevalence was 14% in those with early COPD versus 6% in those without early COPD at baseline examination. Although we cannot completely rule out that some individuals may have developed chronic

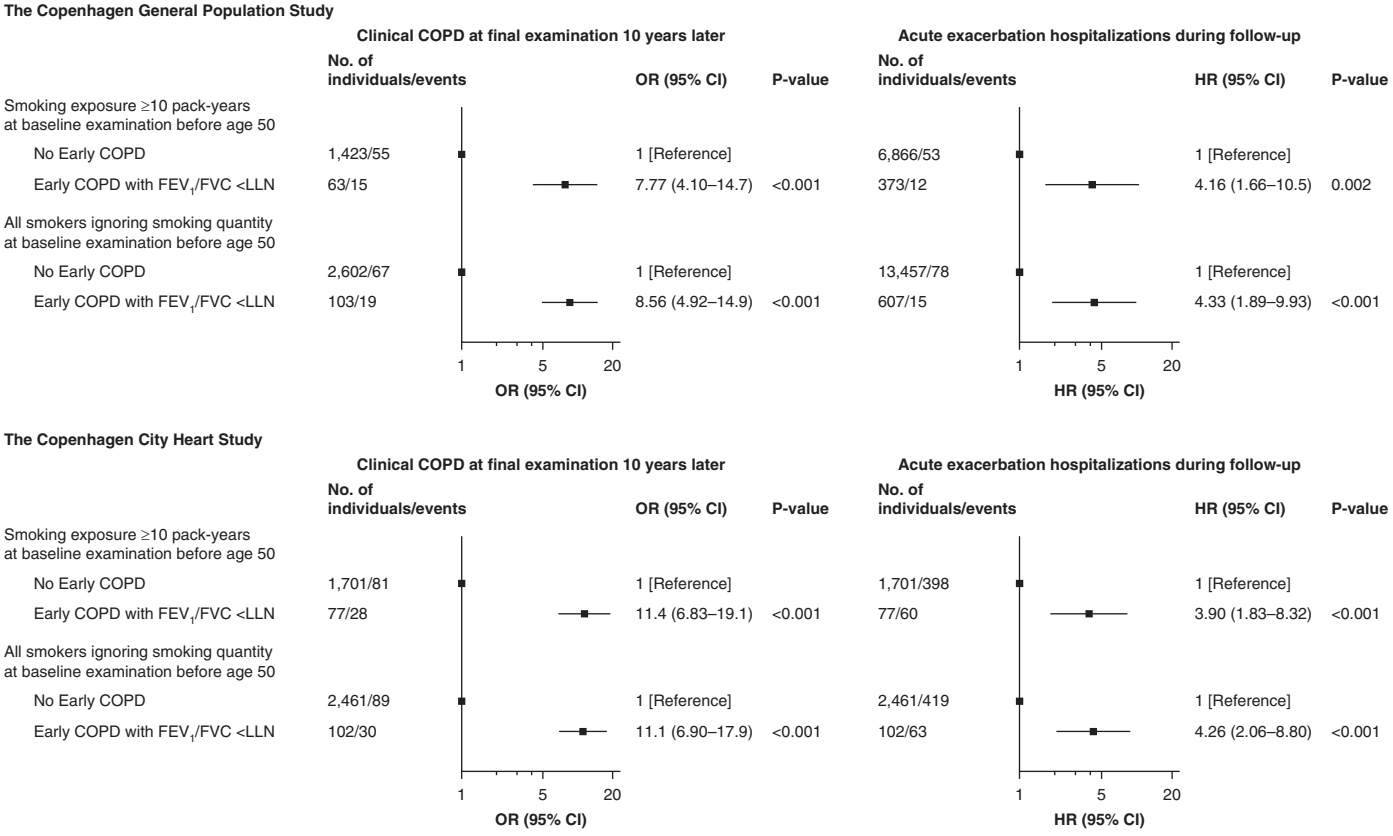

Figure 4. Risk of clinical chronic obstructive pulmonary disease (COPD) at final examination 10 years later and acute exacerbation hospitalizations during follow-up. Clinical COPD was defined as chronic respiratory symptoms with FEV_1/FVC of <0.70 and $FEV_1 < 80\%$ predicted at final examination 10 years later. Chronic respiratory symptoms included chronic mucus hypersecretion, dyspnea, wheezing, and/or cough. The number for the Copenhagen General Population Study varies between the two outcome analyses, as information on lung function at final examination was present for 14,870 individuals, whereas information on hospitalizations during follow-up was present for 89,054 individuals. CI = confidence interval; HR = hazard ratio; LLN = lower limit of normal; OR = odds ratio.

severe asthma during follow-up, which can often be difficult to separate from clinical COPD, the difference in asthma prevalence between those with and without early COPD was more or less similar at the final examination 10 years later. In fact, the difference in asthma prevalence was comparable between early COPD and clinical COPD. Furthermore, it has previously been shown that only a minority of patients with asthma have chronic severe asthma in Denmark after systematic diagnostic assessment (31, 32), again suggesting that chronic severe asthma is unlikely.

Previous studies have mostly investigated mild, but not early, COPD (7, 33). Using the Copenhagen General Population Study, we recently found that 15% fulfil the criteria for early COPD in the general population (defined as FEV_1/FVC $<$LLN in individuals aged $<$50 with smoking exposure $\geq$10 pack-years) (9). Individuals with early COPD more often had chronic respiratory symptoms and severe lung function impairment with an increased risk of acute obstructive lung disease and pneumonia-related hospitalizations and early death. After the exclusion of individuals with FEV_1/FVC $<$0.70 at baseline examination in the present study, 4%, not 15%, seems to fulfill the operational definition of early COPD in the Copenhagen General Population Study (8, 9).

Strengths of the present study include a large contemporary population-based cohort with randomly selected individuals with a long and complete follow-up and essential information on clinical COPD-related outcomes. Furthermore, results were externally validated using another population-based cohort.

A limitation of the present study is that postbronchodilator spirometry was not used to identify early COPD at the baseline examination, nor was it used to identify clinical COPD at the final examination. Thus, some individuals may have a reversible form of airflow limitation, indicating asthma. However, asthma may precede and contribute to COPD development, and the operational definition for early COPD explicitly dictates not to exclude individuals with asthma (8, 34, 35). In addition, clinical COPD was defined as FEV_1/FVC of $<$0.70 and FEV_1 $<$80% predicted, corresponding with moderate to severe airflow limitation, which is usually used as an inclusion criterion for clinical trials with COPD and as an exclusion criterion for clinical trials with asthma (19). This is also the reason why a lower proportion of individuals in this randomly selected population-based cohort developed clinical COPD during 10 years of follow-up, as most COPD cases in the general population often have mild airflow limitation (14).

We have intentionally not defined clinical COPD with a history of exacerbation, as most acute exacerbations of COPD are treated in primary care, and we do not have this information in the present study, which is another limitation. However, it was reassuring to see that results were similar between clinical COPD and acute exacerbation hospitalizations, which can be considered as severe exacerbations of COPD.

Another limitation is survival bias because individuals without lung function information at the final examination had a higher death rate during follow-up versus those with lung function information at final examination. A potential explanation may be the higher baseline age difference, as these two groups only differed slightly when comparing baseline lung function, smoking exposure, and chronic respiratory symptoms. However, survival bias is less likely among younger individuals, as these differences were minute when comparing individuals aged $<$50 years at baseline examination, corresponding with the study population used to define early COPD and predict clinical COPD. In addition, although this may bias clinical COPD as an outcome, acute exacerbation hospitalizations are less biased as an outcome because this information was present on all individuals via the national Danish Patients Registry, in which no person was lost to follow-up.

Clinical implications of the present study relate to early detection and intervention in COPD. A major challenge in COPD is the significant global burden of morbidity and mortality, likely explained by most patients being diagnosed and beginning treatment very late in the disease course (36). Early identification of individuals who will develop COPD will allow the implementation of preventive measures to halt progression and change the disease course accordingly. Our results suggest that defining early COPD is challenging. Depending on the amount of smoking exposure, $<$24% of young adults in the general population with early COPD develop clinical COPD 10 years later. A smoking exposure threshold for early COPD should be reconsidered, as younger individuals are less represented in those with high smoking exposure. ■

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